# Survival benefits of non-surgical triple therapy in hepatocellular carcinoma with inferior vena cava/right atrial tumor thrombus: A retrospective analysis from a multidisciplinary team

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**Abstract.** Hepatocellular carcinoma (HCC) with inferior vena cava and/or right atrial tumor thrombus (IVC/RA TT) is associated with extremely poor prognosis, and the optimal non-surgical treatment approach remains unclear. The current retrospective cohort study aimed to evaluate the efficacy of multidisciplinary team (MDT)-guided non-surgical management in 41 patients with HCC and IVC/RA TT treated at West China Hospital (Sichuan University, Chengdu, China) between January 2019 and December 2023. Patients were categorized according to treatment modality into the following four groups: Systemic therapy alone (n=8), mono-locoregional therapy (n=4), dual-modality therapy (n=14) and triple-modality therapy consisting of systemic therapy, stereotactic body radiation therapy and transarterial chemoembolization (n=15). The triple-modality group displayed significantly longer median overall survival (15 months) and progression-free survival (7 months) compared with the other treatment groups (P=0.019 and P=0.03, respectively). Multivariable Cox regression analysis identified triple-modality therapy as a significant independent protective factor for survival. In addition, this regimen exhibited a favorable safety profile, with no grade ≥3 treatment-related adverse events observed. These preliminary findings suggest that MDT-guided triple-modality combination therapy represents a feasible, safe, and well-tolerated strategy that might offer survival benefits for this high-risk population, although further large-scale validation is necessary.

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*Abbreviations:* AFP, α-fetoprotein; ALBI, albumin-bilirubin (grade); ALT, alanine aminotransferase; AST, aspartate aminotransferase; BCLC, The Barcelona Clinic Liver Cancer (staging classification); ECOG, Eastern Cooperative Oncology Group (performance status); HBV, Hepatitis B virus; HCC, hepatocellular carcinoma; IVC/RA TT, inferior vena cava/right atrial tumor thrombus; MDT, multidisciplinary team; OS, overall survival; PFS, progression-free survival; PIVKA-II, protein induced by vitamin K absence or antagonist-II; PVTT, portal vein tumor thrombus; SBRT, stereotactic body radiation therapy; TACE, transarterial chemoembolization

*Key words:* hepatocellular carcinoma, inferior vena cava, right atrium, tumor thrombus, multidisciplinary team

## Introduction

Hepatocellular carcinoma (HCC) is the 5th most common type of cancer and the 3rd leading cause of cancer-related mortality worldwide, presenting a major public health challenge (1-3). HCC is characterized by highly aggressive biological behavior and a pronounced propensity for vascular (invasion, frequently resulting in the development of tumor thrombus (TT). Although the portal vein is the most commonly involved site, tumor invasion into the hepatic vein, inferior vena cava (IVC), and, in rare cases, the right atrium (RA) may also occur (4). According to the American Association for the Study of Liver Diseases guidelines and the Barcelona Clinic Liver Cancer (BCLC) staging system, HCC with IVC/RA TT is classified as BCLC stage C disease (5). This condition is associated with a poor prognosis due to the increased risk of distant metastasis, pulmonary embolism, cardiac outflow obstruction and multi-organ dysfunction (5-7). Despite notable advances in the management of HCC over the past few decades, the optimal treatment strategy for patients with IVC/RA TT remains controversial. Several retrospective studies conducted in Japan have suggested that surgical resection can provide survival benefit, particularly in the absence of other effective treatment options (8,9). However, surgery in this setting is technically demanding and requires meticulous perioperative management due to the high risk of perioperative mortality (9).

For patients with advanced HCC, current clinical guidelines recommend systemic therapy with sorafenib as the standard first-line treatment due to its established efficacy and safety profile (5). IMbrave150 trial revealed that systemic therapy with atezolizumab plus bevacizumab could achieve prolonged overall survival (OS) and progression-free survival (PFS) compared with sorafenib monotherapy. In addition, other systemic therapy regimens, such as lenvatinib, donafenib and immune checkpoint inhibitors (ICIs) such as nivolumab and pembrolizumab, have also shown survival benefits (7,10,11). Locoregional treatments, including transarterial chemoembolization (TACE) and stereotactic body radiation therapy (SBRT), have also demonstrated promising efficacy with a favorable safety and tolerability profile (12). Furthermore, multidisciplinary team (MDT)-based management has emerged as a key approach for optimizing treatment selection and integrating multimodal therapies in patients with advanced HCC (13,14).

The present study aimed to evaluate the clinical characteristics and treatment outcomes of patients with HCC and IVC/RA TT who underwent non-surgical treatment with MDT participation. The primary objective was to assess the efficacy and safety of these combination therapeutic strategies.

## Materials and methods

*Patient selection*. In this retrospective study, a total of 41 patients with HCC and IVC/RA TT who were admitted to the MDT clinic for HCC with vascular TT at the West China Hospital of Sichuan University (Chengdu, China) between January 2019 and December 2023 were reviewed. The diagnosis of HCC was confirmed using contrast-enhanced CT or MRI. Each scan was independently evaluated by two experienced radiologists, and all imaging examinations were completed ≤2 weeks prior to treatment initiation. The inclusion criteria were as follows: i) Confirmed diagnosis of HCC based on imaging findings; ii) radiological confirmation of the location and extent of IVC or RA TT; iii) Child-Pugh grade A or B and an Eastern Cooperative Oncology Group performance status of 0 or 1; and iv) prior MDT evaluation with complete treatment records available. The exclusion criteria were the following: i) Presence of other primary tumors or metastatic liver cancer; ii) severe liver failure (Child-Pugh grade C); iii) incomplete medical records; and iv) loss to follow-up ≤2 months after initial treatment. For TT classification, the HV/IVC TT system proposed by Cheng Shuqun was applied (15). According to this system, TT was categorized into three types based on its anatomical extent in the IVC: Type I (hepatic venous type), confined to the hepatic vein; Type II (subphrenic), located below the diaphragm in the IVC; and Type III (supraphrenic type), extending above the diaphragm into the RA. Patients and the public were not involved in the design, conduct, reporting or dissemination of the present study.

*Treatment protocols*. All patients received MDT-guided treatment recommendations. The MDT consisted of several experts from the departments of liver surgery, medical oncology, radiation therapy, interventional therapy and imaging. Following comprehensive clinical evaluation and supplementary examinations, individualized treatment plans were developed by the MDT experts based on the specific clinical condition of each patient. Treatment strategies included targeted therapy (sorafenib, lenvatinib and bevacizumab), immunotherapy (camrelizumab, tisleilizumab and atezolizumab), SBRT and TACE. All therapeutic regimens were administered according to established clinical guidelines.

*Follow-up and monitoring*. Patients were regularly monitored to assess treatment response, disease progression and survival outcomes. Follow-up assessments were performed every 3 months during the 1st year after treatment initiation and included clinical evaluation, laboratory testing of liver function and tumor markers and contrast-enhanced imaging examinations (CT or MRI). To ensure consistency across treatment modalities, tumor response and disease progression were independently assessed by two senior radiologists according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST). Disease progression was defined as radiological evidence of enlargement of target tumor lesions, development of new lesions or expansion of the TT based on mRECIST criteria, regardless of the treatment received (16). Any discrepancies between reviewers were resolved by consensus or by a third senior radiologist. Follow-up was maintained until mortality or the end of the study period. The primary endpoint was OS, and the secondary endpoint was PFS. Both survival periods were calculated from the date of treatment initiation to the date of mortality from any cause or the first documented disease progression based on the mRECIST criteria, respectively. Patients who remained alive or free of progression at the final follow-up were censored at the date of their last hospital visit.

*Statistical analysis*. Baseline patient characteristics were summarized using continuous variables, expressed as the mean or median and categorical variables, presented as frequencies and percentages. Comparisons among multiple groups were performed using one-way ANOVA for normally distributed continuous variables and the Kruskal-Wallis test for non-normally distributed data. If statistical significance was observed, Tukey's honest significant difference (HSD) test or Dunn's test was applied for post hoc pairwise comparisons, respectively. Categorical variables were compared using the Pearson $\chi^2$ test or Fisher's exact test, as appropriate. OS and PFS were analyzed utilizing the Kaplan-Meier method and compared using the log-rank test. All statistical tests were two-sided, and $P<0.05$ was considered to indicate a statistically significant difference. In the Cox regression, variables with $P<0.10$ were entered in the multivariable Cox regression model, with a $P<0.05$ considered statistically significant. To minimize overfitting and ensure the stability of the multivariable Cox proportional hazards model in this relatively small cohort, variables with extremely low event frequencies, such as pulmonary embolism, were excluded from the multivariable analysis. All data analyses were conducted using R software version 4.4.1 (R Foundation for Statistical Computing; https://www.R-project.org/).

## Results

*Baseline characteristics*. In the present study, a total of 41 patients diagnosed with HCC and IVC/RA TT were

Table I. Baseline characteristics of hepatocellular carcinoma with IVC/RA TT.

| Characteristics | Value |
|---|---|
| Age, years | 53.46±11.29 |
| Sex, n (%) | |
| Male | 34 (82.93) |
| Female | 7 (17.07) |
| AFP, n (%) | |
| ≤400 ng/ml | 17 (41.46) |
| >400 ng/ml | 24 (58.54) |
| PIVKA-II | |
| ≤1,000 mAU/ml | 5 (12.20) |
| >1,000 mAU/ml | 36 (87.80) |
| ALT, n (%) | |
| ≤40 U/l | 18 (43.90) |
| >40 U/l | 23 (56.10) |
| AST, n (%) | |
| ≤40 U/l | 9 (21.95) |
| >40 U/l | 32 (78.05) |
| TB, μmol/l | 25.2 (15.5-37.6) |
| Ab, g/l | 39.49±4.88 |
| ALBI, n (%) | |
| Grade1 | 14 (34.15) |
| Grade2 | 27 (65.85) |
| Child-Pugh stage, n (%) | |
| A | 32 (78.05) |
| B | 9 (21.95) |
| Cirrhosis, n (%) | |
| No | 7 (17.07) |
| Yes | 34 (82.93) |
| Hepatitis, n (%) | |
| No | 39 (95.12) |
| HBV | 2 (4.87) |
| Tumor number, n (%) | |
| ≤3 | 9 (21.95) |
| >3 | 32 (78.05) |
| Tumor diameter, n (%) | |
| ≤10 cm | 22 (53.66) |
| >10 cm | 19 (46.34) |
| Intrahepatic metastasis, n (%) | |
| No | 4 (9.76) |
| Yes | 37 (90.24) |
| Lymph metastasis, n (%) | |
| No | 31 (75.61) |
| Yes | 10 (24.39) |
| Metastasis, n (%) | |
| No | 21 (51.22) |
| Yes | 20 (48.78) |
| CNLC stage, n (%) | |
| IIIa | 21 (51.22) |
| IIIb | 20 (48.78) |
| PVTT, n (%) | |
| No | 12 (29.27) |
| I | 2 (4.87) |
| II | 9 (21.95) |
| III | 16 (39.02) |
| IV | 2 (4.87) |
| IVC/RA TT, n (%) | |
| I | 22 (53.66) |
| II | 8 (21.95) |
| III | 11 (24.39) |
| Pulmonary embolism, n (%) | |
| No | 39 (95.12) |
| Yes | 2 (4.87) |
| Treatment, n (%) | |
| S | 8 (19.51) |
| T/R | 4 (9.76) |
| S+T/R | 14 (34.15) |
| S+T+R | 15 (36.59) |

S, systemic therapy; TACE, transarterial chemoembolization; SBRT, stereotactic body radiation therapy; T/R, TACE or SBRT; S+T/R, systemic therapy combined with T/R; S+T+R, triple-modality therapy consisting of systemic therapy, TACE, and SBRT.

enrolled. The median follow-up duration was 10 months (range, 4-14 months), during which 31 mortalities (75.61%) were recorded. Key baseline characteristics, including age, sex, liver function parameters, tumor burden and underlying liver diseases, are summarized in Table I. According to the IVC/RA TT classification, 22 patients (53.66%) were classified as type I, eight (19.51%) as type II and 11 (26.83%) as type III. PVTT was also common in this cohort. Particularly, two patients (4.87%) exhibited type I PVTT, nine (21.95%) had type II, 16 (39.02%) had type III, two (4.87%) had type IV, whereas 12 (29.27%) showed no evidence of PVTT. Extrahepatic metastasis was observed at first presentation in 20 patients (48.78%), with the lungs, adrenal glands, peritoneum and bones representing the most common metastatic sites. Regarding treatment modalities, eight patients (19.51%) received systemic therapy alone (S), four (9.76%) received mono-locoregional therapy with either SBRT or TACE (T/R), 14 (34.15%) received dual therapy (S + T/R) and 15 (36.59%) received triple therapy consisting of systemic therapy combined with SBRT and TACE (S + R + T). Detailed information regarding the specific treatment combinations and sequential alterations in the triple-modality therapy group is presented in Table SI. No statistically significant differences in baseline characteristics were observed among the different treatment groups (Table SII).

*OS and PFS analysis in patients with HCC and IVC/RA TT.* Follow-up was completed for all patients and concluded in December 2024. The median OS for the entire cohort

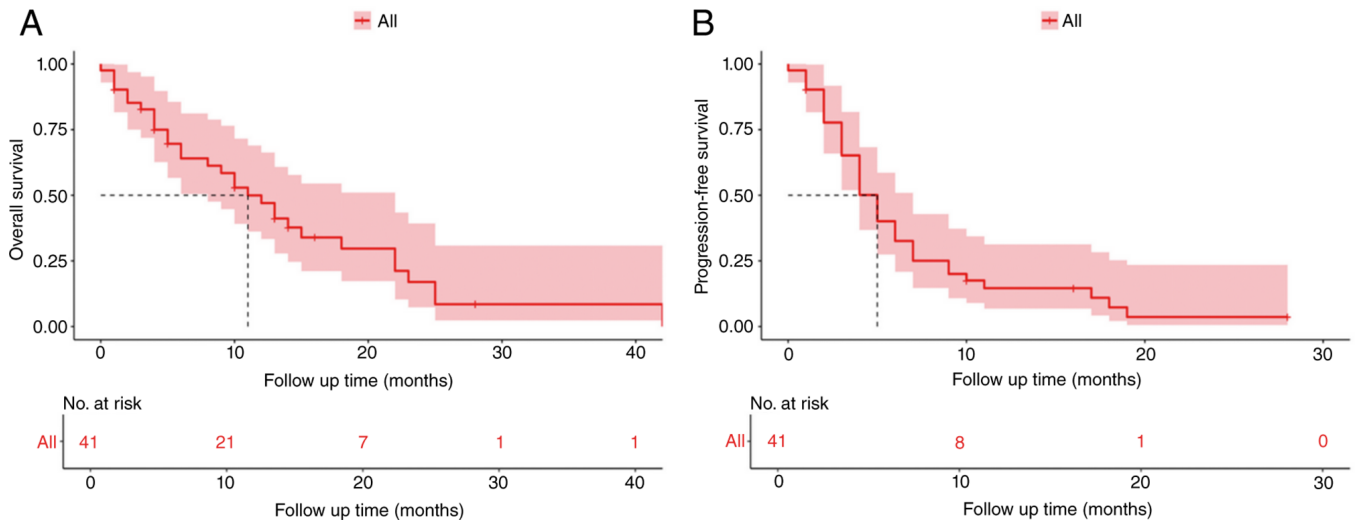


Figure 1. Kaplan-Meier curves of (A) overall survival and (B) progression-free survival for the entire cohort of patients.

was 11 months [95% confidence interval (CI), 8-22 months], with OS rates of 82.7, 64.0 and 47.0% at 3, 6 and 12 months, respectively (Fig. 1A). The median PFS was 5 months (95% CI, 4-7 months), with PFS rates of 65.2, 32.6 and 14.6% at 3, 6 and 12 months, respectively (Fig. 1B). Patients with distant metastasis exhibited significantly worse survival outcomes compared with those without metastasis (median OS, 8 months; 95% CI, 5-15 months vs. 18 months; 95% CI, 13 months-NR; P=0.0071; Fig. 2A). The 3-, 6- and 12-month OS rates were 80.0, 53.8 and 26.9% in patients with metastasis compared with 85.2, 74.6 and 68.3% in the non-metastatic group. Median PFS was 4 months (95% CI, 3-7 months) in the metastatic group and 6 months (95% CI, 3-17 months) in the non-metastatic group (Fig. 2B), though this difference did not reach statistical significance (P=0.11). Stratified analyses according to the anatomical extent of the thrombus revealed that patients with type III IVC/RA TT or RATT extension tended to have worse survival outcomes (Fig. 2C-F). However, these differences did not reach statistical significance for either OS or PFS (all P>0.05).

*Efficacy of different treatment groups in patients with HCC and IVC/RA TT.* Median OS varied significantly across different treatment groups (P=0.019; Fig. 3A). Patients treated with systemic therapy alone had a median OS of 4 months (95% CI, 4 months-NR), while those receiving mono-locoregional therapy achieved a median OS of 5.5 months (95% CI, 0 months-NR). Patients treated with dual therapy showed a median OS of 9 months (95% CI, 4 months-NR), whereas those receiving triple therapy achieved the longest median OS of 15 months (95% CI, 12 months-NR). A similar pattern was also observed for PFS (P=0.03; Fig. 3B). Similarly, median PFS was 3 months (95% CI, 3 months-NR) in the systemic therapy alone group, 2.5 months (95% CI, 0 months-NR) in the mono-locoregional therapy group, 4 months (95% CI, 2 months-NR) in the dual therapy group and 7 months (95% CI, 5 months-NR) in the triple-modality therapy group.

*Prognostic factors of OS and PFS.* Univariable and multivariable Cox regression analyses were performed to identify prognostic factors associated with OS and PFS. To ensure model stability in this small cohort, pulmonary embolism was excluded from the multivariable model due to its extremely low event rate. For OS, multivariable analysis revealed that the choice of treatment regimen was an independent prognostic factor (Table II). Compared with triple therapy (S + T + R), both systemic therapy alone [S; hazard ratio (HR), 4.31; 95% CI, 1.25-14.83; P=0.021] and mono-locoregional therapy (T/R; HR, 5.73; 95% CI, 1.33-24.62; P=0.019) were independently associated with a higher risk of mortality. Additionally, the presence of distant metastasis was confirmed as an independent risk factor for worse OS (HR, 2.73; 95% CI, 1.17-6.39; P=0.021). For PFS, multivariable analysis indicated that mono-locoregional therapy (T/R; HR, 5.89; 95% CI, 1.51-22.94; P=0.011), dual therapy (S + T/R; HR, 4.24; 95% CI, 1.55-11.62; P=0.005) and tumor diameter >10 cm (HR, 3.94; 95% CI, 1.79-8.65; P<0.001) were independent predictors of disease progression (Table SIII).

## Discussion

Patients with HCC and IVC/RA TT generally face a poor prognosis due to extensive intrahepatic tumor burden and the limited availability of therapeutic options (17). In the present study, the results demonstrated that patients undergoing triple therapy (systemic therapy combined with SBRT and TACE) achieved a significantly prolonged median OS of 15 months compared with those treated with single- or dual-modality therapy. Notably, this triple therapy showed a favorable safety profile, as no grade ≥3 treatment-related adverse events were reported, indicating robust tolerability in this clinically advanced and vulnerable patient cohort.

Historically, surgical resection has been considered the primary radical treatment option for these advanced cases. However, its clinical utility remains limited. A previous large-scale multicenter study from Japan demonstrated that although surgery could achieve a median survival of 1-2 years,

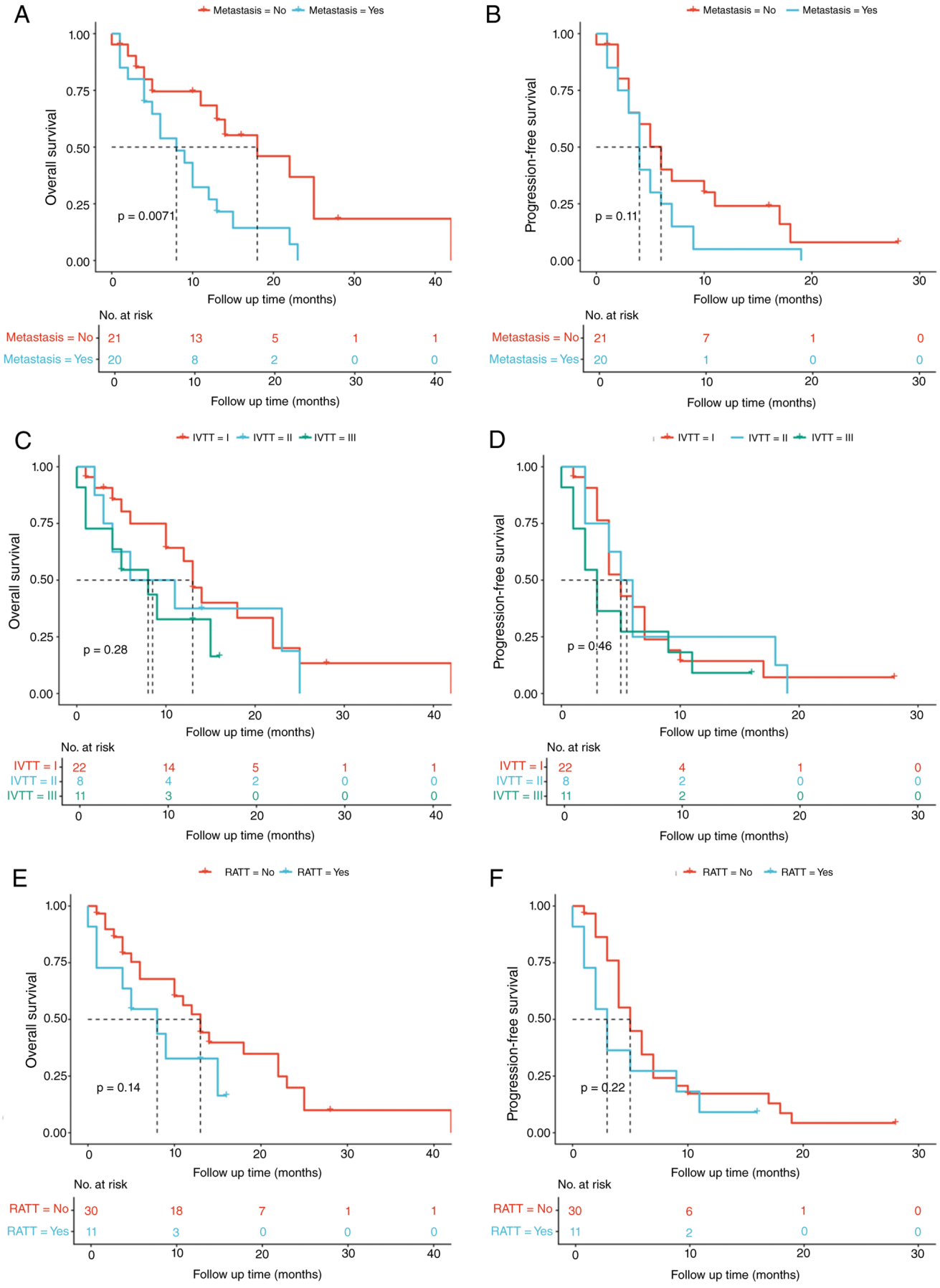


Figure 2. Kaplan-Meier curves of (A) overall survival and (B) progression-free survival for the entire cohort of patients with or without metastasis; Kaplan-Meier curves of (C) overall survival and (D) progression-free survival for the entire cohort of patients with different type of IVC TT; Kaplan-Meier curves of (E) overall survival and (F) progression-free survival for the entire cohort of patients with or without RA TT. IVTT, inferior vena cava tumor thrombus; RA TT, right atrial tumor thrombus.

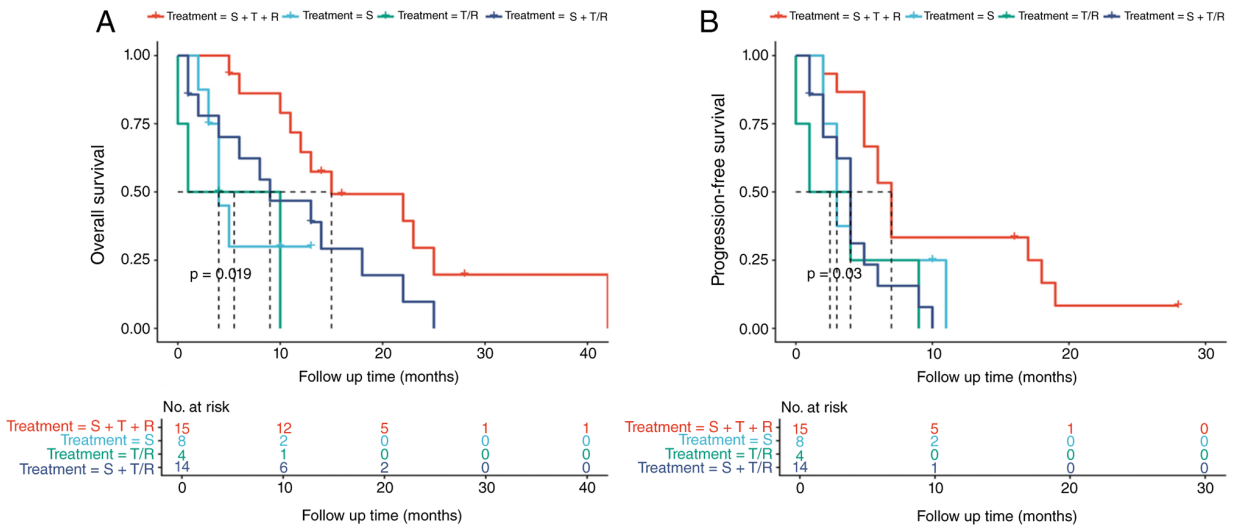


Figure 3. Kaplan-Meier curves of (A) overall survival and (B) progression-free survival for the entire cohort of patients in different treatment groups. S, systemic therapy; TACE, transarterial chemoembolization; SBRT, stereotactic body radiation therapy; T/R, TACE or SBRT; S+T/R, systemic therapy combined with T/R; S+T+R, triple-modality therapy consisting of systemic therapy, TACE, and SBRT.

it was accompanied by a remarkably high recurrence rate (median time to recurrence, 0.48 years) and considerable perioperative mortality (9). Surgery in this setting is technically demanding and carries substantial risks of severe complications, including massive hemorrhage, liver failure and pulmonary embolism (9,18,19). Given that the majority of patients with IVC/RA TT present with impaired liver reserves and extensive tumor burden, several are inherently ineligible for such highly invasive interventions. Therefore, the development of effective non-surgical treatment approaches with low toxicity represents a key unmet clinical need for patients with advanced HCC. The results of the present study suggested that triple therapy could serve as a viable and safe therapeutic alternative for this high-risk population, providing significant survival benefits while avoiding the substantial risks associated with aggressive surgical intervention.

The rationale for non-surgical treatment approaches has been further strengthened by the rapid evolution of systemic oncology. Since sorafenib was established as the first-line standard therapy in 2007 (17,20,21), the therapeutic landscape has evolved substantially with the introduction of ICIs. Agents targeting cytotoxic T-lymphocyte-associated antigen 4, programmed cell death protein (PD-1) or PD-1 ligand 1 can enhance intratumoral T cell infiltration, thereby amplifying antitumor immune responses (22-24). Landmark clinical trials, including HIMALAYA (tremelimumab plus durvalumab) and IMbrave150 (atezolizumab plus bevacizumab), demonstrated notably improved OS and PFS compared with sorafenib monotherapy, while also preserving patient quality of life (25-27).

Nevertheless, systemic therapy alone commonly shows limited efficacy in patients with large-volume and obstructive tumor thrombi. This limitation underscores the necessity of integrating locoregional interventions to achieve synergistic local and systemic control. Interventional therapies, such as TACE, can directly reduce tumor burden by embolizing tumor-supplying arteries (13,28,29). Concurrently, SBRT can induce precise DNA damage and apoptosis within the thrombus area (30-32). In addition to its cytotoxic effects, localized radiotherapy can promote the release of tumor-related antigens, thereby transforming the cold tumor microenvironment and markedly enhancing the efficacy of systemic immunotherapy (30-32). Emerging clinical evidence supports this synergy. For example, the combination of TACE with lenvatinib and PD-1 inhibitors has yielded substantial improvements in objective response rates and survival outcomes (28). Similarly, combining SBRT with systemic therapy could notably improve PFS in patients with locally advanced HCC (30).

For patients with IVC/RA TT, balancing the efficacy of multimodal treatment against cumulative toxicity is clinically important. The findings of the present study align with those of previous ones indicating that combining targeted therapies with ICIs can maintain a manageable safety profile, with common side effects, including hypertension, fatigue and hand-foot syndrome, easily mitigated through supportive care or dose modification (25,26,33,34). Additionally, the incorporation of SBRT and TACE introduces minimal severe toxicities, as post-embolization syndrome and transient elevations in liver enzyme levels are commonly self-limiting or easily managed by experienced clinicians (31,32). Collectively, the aforementioned findings suggested that multimodal non-surgical regimens could offer a favorable therapeutic index for these high-risk cohorts, holding the potential to achieve meaningful tumor control comparable to that of surgical interventions, while markedly reducing the risk of severe complications.

MDT management plays a key role in the successful application of these complex treatment combinations. By integrating expertise across liver surgery, oncology, hepatology, interventional radiology and radiotherapy, the MDT approach enables personalized, timely and well-balanced interventions (13,14,35,36). However, a key limitation of MDT-guided allocation is the inherent risk of selection bias. Because treatment decisions in this retrospective cohort were based on multidisciplinary consensus rather than prospective randomization, the improved survival outcomes observed in the

Table II. Univariable and multivariable analysis of variables for OS.

| | Univariable analysis | | Multivariable analysis | |
|---|---|---|---|---|
| Variable | HR (95% CI) | P-value | HR (95% CI) | P-value |
| Age | | | | |
| >50 vs. ≤50 years | 0.61 (0.29-1.32) | 0.21 | | |
| Sex | | | | |
| Male vs. female | 0.73 (0.27-1.93) | 0.52 | | |
| AFP | | | | |
| >400 vs. ≤400 ng/ml | 1.08 (0.52-2.23) | 0.84 | | |
| PIVKA-II | | | | |
| >1,000 vs. ≤1,000 mAU/ml | 0.95 (0.33-2.77) | 0.93 | | |
| ALT | | | | |
| >40 vs. ≤40 U/l | 1.16 (0.56-2.39) | 0.69 | | |
| AST | | | | |
| >40 vs. ≤40 U/l | 2.48 (0.94-6.52) | 0.07 | 2.06 (0.72-5.87) | 0.178 |
| ALBI | | | | |
| Grade 2 vs. Grade 1 | 1.59 (0.72-3.50) | 0.25 | | |
| Child Pugh stage | | | | |
| B vs. A | 1.03 (0.42-2.53) | 0.95 | | |
| Cirrhosis | | | | |
| Yes vs. No | 0.81 (0.28-2.39) | 0.71 | | |
| Hepatitis | | | | |
| HBV vs. No | 0.66 (0.15-2.83) | 0.58 | | |
| Tumor number | | | | |
| >3 vs. ≤3 | 0.94 (0.42-2.11) | 0.88 | | |
| Tumor diameter | | | | |
| >10 vs. ≤10 cm | 1.48 (0.72-3.05) | 0.29 | | |
| Intrahepatic metastasis | | | | |
| Yes vs. No | 1.01 (0.35-2.92) | 0.99 | | |
| Lymph metastasis | | | | |
| Yes vs. No | 1.75 (0.76-4.00) | 0.19 | | |
| Metastasis | | | | |
| Yes vs. No | 2.85 (1.30-6.28) | 0.01[a] | 2.73 (1.17-6.39) | 0.021[a] |
| PVTT | | | | |
| I vs. No | 0.65 (0.08-5.17) | 0.68 | | |
| II vs. No | 0.77 (0.29-2.09) | 0.61 | | |
| III vs. No | 0.96 (0.40-2.34) | 0.94 | | |
| IV vs. No | 2.97 (0.61-14.48) | 0.18 | | |
| IVTT | | | | |
| II vs. I | 1.34 (0.54-3.31) | 0.52 | | |
| III vs. I | 2.02 (0.82-4.96) | 0.12 | | |
| RATT | | | | |
| Yes vs. No | 1.86 (0.79-4.37) | 0.15 | | |
| Pulmonary embolism | | | | |
| Yes vs. No | 10.43 (2.00-54.31) | 0.01 | | |
| Treatment | | | | |
| S vs. S+T+R | 3.68 (1.14-11.84) | 0.029[a] | 4.31 (1.25-14.83) | 0.021[a] |
| T/R vs. S+T+R | 6.53 (1.63-26.15) | 0.008[b] | 5.73 (1.33-24.62) | 0.019[a] |
| S+T/R vs. S+T+R | 2.28 (0.97-5.35) | 0.058 | 2.08 (0.88-4.89) | 0.094 |

[a]P<0.05, [b]P<0.01. S, systemic therapy; TACE, transarterial chemoembolization; SBRT, stereotactic body radiation therapy; T/R, TACE or SBRT; S+T/R, systemic therapy combined with T/R; S+T+R, triple-modality therapy consisting of systemic therapy, TACE, and SBRT.

triple-modality therapy group could partially reflect a clinical bias toward patients with improved baseline performance and improved-preserved liver function.

The present study provided a valuable, detailed evaluation of individualized sequencing strategies for systemic and locoregional therapies in a rare patient population. Nevertheless, several limitations should be acknowledged. First, the retrospective and MDT-driven nature of the present study introduced inherent selection bias. However, this concern was largely mitigated by the lack of statistically significant differences in key pre-treatment baseline characteristics among the different treatment groups (P>0.05; Table SI). Second, the clinical rarity of IVC/RA TT limited the sample size, thereby reducing the statistical power of subgroup analyses. Third, the therapeutic heterogeneity among combination regimens could introduce variability in outcome assessment. However, such treatment adaptations could reflect the clinical reality, in which tailored precision medicine strategies within an MDT framework could ensure patient safety in this hyper-advanced cohort. Lastly, as this was a single-center study, the generalizability of the findings requires further validation in larger prospective multicenter cohorts.

In conclusion, the present study demonstrated that a multimodal non-surgical approach, particularly triple-modality therapy integrating systemic therapy, SBRT and TACE under MDT management, could provide promising survival benefits with an excellent safety profile for patients with HCC and advanced IVC/RA TT. By achieving notable tumor control with manageable toxicity, this multidisciplinary regimen could serve as a feasible alternative to highly invasive surgical interventions. These findings could offer valuable clinical insights into individualized treatment sequencing and help inform the design of future prospective trials aimed at optimizing therapeutic strategies for this high-risk patient population.

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**Availability of data and materials**

The data generated in the present study may be requested from the corresponding author.

**Authors' contributions**

PT contributed to the conception and design of the study, data collection and assembly, data analysis and interpretation, and manuscript drafting. JL contributed to the provision of patient data, critical revision of the manuscript for important intellectual content, language editing and data analysis. JD made substantial contributions to the acquisition, assembly and quality control of the data. XW and JZ were responsible for the conception of the study, and the substantial acquisition and validation of study materials and clinical patient data. YY and YZ provided administrative and financial support, supervised the entire study, made substantial contributions to the conception of the project and the critical interpretation of data, critically revised the manuscript for important intellectual content, and gave final approval of the version to be published. All authors have read and approved the final manuscript. PT, JZ and YY confirm the authenticity of all the raw data.

**Ethics approval and consent to participate**

This retrospective cohort study was conducted in accordance with the Declaration of Helsinki (approval no. 2025-Review-2783) and was approved by the Institutional Review Board (or Ethics Committee) of West China Hospital of Sichuan University (Chengdu, China). The requirement for informed consent was waived by the IRB due to the retrospective nature of the present study and the use of anonymized patient data.

**Patient consent for publication**

Patient consent for publication was waived by the Institutional Review Board due to the retrospective nature of the study and the use of anonymized patient data.

**Competing interests**

All authors declare that they have no competing interests.

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